**Acetaminophen in Cancer Pain**

**To the Editor:** A nonopioid (such as paracetamol or a nonsteroidal anti-inflammatory drug) was added as an essential component of step 2 of the revised version of the WHO analgesic ladder to reflect the relatively low analgesic potential of the “weak” opioids (codeine and dextropropoxyphene). This supports the use of combined preparations (eg, paracetamol/codeine and paracetamol/dextropropoxyphene). The use of paracetamol as an adjunct to “strong” opioids such as morphine is optional at step 3 of the WHO ladder but has become entrenched in palliative care “folklore,” despite little evidence of its benefit.

The article by Stockler et al is well designed and takes into account many of the problems inherent in palliative care research (eg, the need for short study times, easy assessments, and telephone follow-up). The conclusion, however, that paracetamol improves pain in cancer patients already taking opioids is not well supported by the data presented. The only significant result in favor of adding paracetamol to the analgesic regimen was an average difference on two assessment days of 0.4 on an 11-point verbal numeric scale of pain ($P = .03$). One must question the clinical benefit of this. No other pain end point (Visual Analog Scale for pain, patient preference, and need for breakthrough medications) was statistically different. In addition, there was no difference in the balance between analgesia and adverse effects as measured by nausea and vomiting, drowsiness, and constipation scores. Although the average increase in overall well-being was just significant at the $P = .05$ level, this is arguably the softest outcome measure, as the determinants of well-being are multifactorial.

The requirement of palliative patients to swallow an additional 10 large tablets a day for an uncertain clinical outcome may be considered a burdensome treatment. Certainly, in Australia, full compliance with this protocol would be problematic, as the public is well informed of the dangers to hepatic function with paracetamol doses exceeding 4 g/d.

We consider that this study needs to be repeated in a larger number of patients and stratified according to the daily morphine-equivalent dose. Our hypothesis is that paracetamol may be of greater benefit to those on lower opioid doses, thus supporting the current WHO analgesic ladder recommendations.

**IN REPLY:** Period analysis resulted in estimates of 40-year absolute and relative (absolute/population) survival curves. The Methods section of the article by Brenner and Hakulinen states that the estimates are intended to reflect cumulative survival experience for newly diagnosed patients. It is not clear how this differs from “current estimates of long-term survival expectations.”

Patients diagnosed 40 years ago did remain at increased risk of death through the 1990s, as demonstrated by relative conditional probabilities by decade. This point does not depend on period analysis, which uses conditional probabilities from the past for projections into the future. To the extent that the past conditional probability estimates will no longer apply, we cannot rely on the accuracy of the projections in the coming decades, empirical observations from previous decades notwithstanding.

The implausible assumption of a cure for death would indeed have provided a striking but irrelevant example. I sincerely hope the breast cancer cure scenario is neither implausible nor irrelevant.

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The author indicated no potential conflicts of interest.

**REFERENCES**


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unconvincing on their own, but also favor acetaminophen. Improvements in pain, overall well-being, and strength of preference for acetaminophen were highly correlated with one another (Spearman’s rank correlations 0.49 to 0.8; all P < .007). Differences in nausea, vomiting, drowsiness, constipation, and breakthrough doses were not expected for a 48-hour intervention that held baseline doses of opioids constant.

The dose we tested (10 tablets per day, 1 g every 4 hours while awake) was based on acetaminophen’s half-life and the usual dosing intervals for short-acting morphine. A lower dose of 8 tablets per day (1 g every 6 hours) is commonly used with long-acting opioids in people with cancer pain, and as an alternative to nonsteroidal anti-inflammatory drugs in people with degenerative joint disease. Hepatic toxicity is rare with doses less than 8 g daily, even in patients with chronic liver disease.

We stand by our conclusion that the addition of acetaminophen is worth considering in all people with persistent cancer pain, despite a strong opioid regimen. Little is lost by letting such people try acetaminophen for a few days so that they can decide for themselves if the benefits are worth the extra tablets.

Heterogeneity of practice (and prejudice) is common and provides a strong rationale for clinical trials. Studies of interventions for cancer pain are sorely needed. Trials testing a lower dose of acetaminophen for a longer duration in patients using a wide range of strong opioids and coanalgesics would be particularly welcome.

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Regarding “Abbreviated Course of Radiation Therapy in Older Patients with Glioblastoma Multiforme: A Prospective Randomized Clinical Trial”

To the Editor: Roa et al recently presented the results of a randomized trial comparing standard (60 Gy in 30 fractions) with short-course (40 Gy in 15 fractions) radiotherapy (RT) in the treatment of elderly patients (defined as older than 60 years) with glioblastoma multiforme (GBM).

Outcomes were similar with respect to overall survival (median, 5.4 months); however, quality-of-life comparisons were not possible because of incomplete data. An accompanying Editorial by Shaw in the same issue discusses the Radiation Therapy Oncology Group stratification of high-grade gliomas (first modeled by Curran et al) and concludes that elderly patients (defined as older than 50 years) with low Karnofsky performance status (ie, < 70) who are neurologically impaired and who have been treated surgically by biopsy can reasonably only be offered short-course RT (accelerated hypofractionated RT). However, not mentioned in either article is an alternative treatment—that of treating the elderly with GBM with primary chemotherapy.

Except for a few studies, the elderly cohort has been ignored, notwithstanding the fact that this group constitutes 20% to 25% of all patients presenting with GBM. According to these studies (referenced in Roa et al), elderly patients have poor survival, with median survival ranging from 4 to 6 months. By and large, these studies have used RT as primary therapy and continue to advocate for RT in the treatment of elderly patients. However, RT is not a trivial treatment for the elderly patient. Published studies indicate that as many as 50% of elderly patients may not receive treatment. In a previous retrospective study of 86 consecutive patients, we demonstrated that elderly patients (defined as ≥ 70 years of age) with GBM had equivalent survival when treated with either standard RT or monthly temozolomide (TMZ; 4.1 v months median survival; 9.3% v 11.9% 1-year survival). TMZ was well tolerated, and patients maintained excellent performance status for several months. Such a result is unusual after RT, as elderly patients almost always develop excessive fatigue and frequent worsening of neurologic deficits.

There are strong clinical, economic, and social imperatives for determining the optimal age-specific treatment approach for GBM. A randomized controlled trial (such as that performed by Roa et al) is the best way to obtain that information, and we would advocate a trial comparing short-course RT to TMZ in elderly patients with GBM. In the meantime, we believe based on our study that it is appropriate to offer TMZ to elderly patients with newly diagnosed GBM as an alternative to RT as first-line therapy.

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